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10/624,909	07/21/2003	Eileen Tozer	564462005300	7087

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EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
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1637

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/624,909

Applicant(s)

TOZER ET AL.

Examiner

Angela Bertagna

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☒ Claim(s) 189 is/are allowed.
- 6) ☒ Claim(s) 1, 14, 15, 29, 33, 35, 40, 34-45, 48, 49, 87, 188, 192, 203-207, 217, 218, 225-228 is/are rejected.
- 7) ☒ Claim(s) 225 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 1,14,15,29,33,35,40,42-45,48,49,51,54,56,58,87,106,107,111,113,116,138,143,174,175,177,182,184,187-190,192,203-208 and 215-231.
Continuation of Disposition of Claims: Claims withdrawn from consideration are
42,51,54,56,58,106,107,111,113,116,138,143,174,175,177,182,184,187,190,208,215,216 and 219-224.

FINAL REJECTION

Status of the Application

1. Applicant's response filed October 16, 2006 is acknowledged. Claims 1, 14, 15, 29, 33, 35, 40, 42-45, 48, 49, 51, 54, 56, 58, 87, 106, 107, 111, 113, 116, 138, 143, 174, 175, 177, 182, 184, 187-190, 192, 203-208, and 215-231 are currently pending. Claims 42, 51, 54, 56, 58, 106, 107, 111, 113, 116, 138, 143, 174, 175, 177, 182, 184, 187, 190, 208, 215, 216, 219-224 are withdrawn.

Election/Restrictions

2. Newly submitted claims 229-231 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims recite nucleic acid SEQ ID Nos: different from elected SEQ ID NO: 29. As discussed in the previous restriction requirement, each nucleic acid sequence constitutes an independent and distinct invention, because no common structural core is shared between the different sequences (i.e. they each have different nucleotide sequences). Also, the different nucleic acids have different functional properties (i.e. they encode different proteins).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 229-231 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 42, 51, 54, 56, 58, 106, 107, 111, 113, 116, 138, 143, 174, 175, 177, 182, 184, 187, 190, 208, 215, 216, and 219-224 drawn to an invention nonelected with traverse in Paper No. 20060710. A complete reply to the final rejection must include

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cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claim Objections

3. Claim 225 is objected to because of the following informalities: This claim depends from a withdrawn claim (claim 138). Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 15, 29, 33, 35, 40, 43-45, 48, 49, 87, 188, 192, 203-207, 217, 218, and 225-228 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP notes, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1996 (Fed. Cir. 1997)."

In the instant case, independent claim 1 recites "an isolated, synthetic, or recombinant nucleic acid comprising a nucleic acid sequence having at least 75% sequence identity to the

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nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues.” SEQ ID NO: 29 is 687 nucleotides in length. There are approximately 7.2×10^{274} different sequences with 75% identity to the instant SEQ ID NO: 29. This is a very large genus whose members inherently possess different structural and functional properties.

Regarding genus claims, MPEP notes, “For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

“A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure “indicates that the patentee has invented species sufficient to constitute the gen[us].” See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)(“[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from species other than those specifically enumerated.”). “A patentee will not be

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deemed to have invented invention of any species other than the one disclosed.” In re Curtis, 354 F3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)”

Applicant discloses SEQ ID NO: 29, which encodes a green fluorescent protein.

Applicant further discloses related nucleic acid sequences (for example, SEQ ID NO: 1-197 (odd SEQ IDs only), but these sequences share a very high level of identity (greater than 75%), and therefore, do not constitute a representative number of species in the very broad genus outlined above. Furthermore, Applicant does not demonstrate that all of the members of even the described narrow subgenus share a common function. The examples on pages 155-159 teach exemplary methods, and the drawings only depict the fluorescence properties of two proteins. Therefore, since Applicant only teaches nucleic acid sequences with a very high level of identity to the instant SEQ ID NO: 29, with little or no teaching as to their functional properties, and presents no discussion in terms of structural or functional characteristics of sequences with only 75% identity to SEQ ID NO: 29, it must be concluded that the requirement to disclose a representative number of species in the broad genus of claim 1 has not been met (see above), and therefore, at the time of filing, Applicant did not have possession of the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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6. Claims 1, 14, 29, 33, 35, 188, and 192 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AF401282 (submitted by Lesser et al. on August 5, 2001; cited previously).

Regarding claim 1, Lesser teaches an isolated, synthetic, or recombinant nucleic acid encoding a fluorescent protein, comprising a nucleic acid sequence having at least 75% sequence identity to the nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues. See the alignment generated using the BLAST algorithm presented below which demonstrates that Lesser teaches a sequence with 75% identity to the instant SEQ ID NO: 29 over a region of 206 contiguous residues. As noted above, the phrase "at least about 700 contiguous residues" does not define a minimal number of residues that are "at least about 700 contiguous residues." Therefore, the teachings of Lesser anticipate the instant claim 1.

Score = 83.4 bits (43), Expect = 1e-12
Identities = 155/206 (75%), Gaps = 3/206 (1%)
Strand=Plus/Plus

```
(SEQ 29)  97 CCTTACGAAGGAACACAGACTTTACATCTTACAGAGAAGGAAGGCAAGCCTCTGACGTTT 156
          ||||| ||| ||||| ||||| | | ||||| || ||||| ||||| | |||
Lesser    180 CCTTTCGAGGGAACACAGAGCATGGACCTTACAGTCAAAGAAGGCGCGCCTCTGCCTTTT 239

(SEQ 29)  157 TCTTTCGATGTATTGACACCAGCATTTTCAGTATGGAAACCGTACATTACCAAATACCCA 216
          ||| |||| | ||||| ||| || | || ||| | || ||||| |||
Lesser    240 GCTTACGATATCTTGACAACAGTATTCGATTACGGCAACAGGGTATTTGCCAAATACCCA 299

(SEQ 29)  217 GGCAATATACCAGACTTTTTCAAGCAGACCGTTTCTGGTGGCGGGTATACCTGGGAGCGA 276
          ||||| ||||| ||||| ||||| ||||| || ||||| ||||| |||
Lesser    300 CAAGATATACCAGACTATTTCAAGCAGA-CGTTTC--CTGAGGGGTATTCCTGGGAACGA 356

(SEQ 29)  277 AAAATGACTTATGAGGACGGGGGCAT 302
          | ||||| || ||| |||||
Lesser    357 AGCATGACTTACGAAGACCAGGGCAT 382
```

Regarding claim 14, the sequence taught by Lesser encodes a green fluorescent protein (see definition).

ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
 seq_29 687 nt vs.
 gi_15081471_gb_AF401282.1_AF401282 Montastraea fa 683 nt
 scoring matrix: DNA, gap penalties: -16/-4
 70.1% identity; Global alignment score: 1488

	10	20	30	40	50	60
seq_29	ATGAAGGGGGTGAAGGAAGTAATGAAGATCAGTCTGGAGATGGACTGCACTGTTAACGGC					
gi_15081471_	ATGAGTGTGATAAAACCAGACATGAAGATCAAGCTGCGTATGGAAGGCGCTGTAAACGGG					
	10	20	30	40	50	60
seq_29	GACAAATTTTAAGATCACTGGGGATGGAACAGGAGAACCTTACGAAGGAACACAGACTTTA					
gi_15081471_	CACAAGTTCGTGATTGAAGGAGACGGAAGGGCAAGCCTTTTCGAGGGAACACAGAGCATG					
	70	80	90	100	110	120
seq_29	CATCTTACAGAGAAGGAAGGCAAGCCTCTGACGTTTCTTTTCGATGTATTGACACCAGCA					
gi_15081471_	GACCTTACAGTCAAAGAAGGCGCGCCTCTGCCTTTTGCTTACGATATCTTGACAACAGTA					
	130	140	150	160	170	180
seq_29	TTTCAGTATGGAACCGTACATTACCAAATAACCCAGGCAATATACCAGACTTTTTTCAAG					
gi_15081471_	TTCGATTACGGCAACAGGGTATTTGCCAAATACCCACAAGATATACCAGACTATTTTCAAG					
	190	200	210	220	230	240
seq_29	CAGACCGTTTCTGGTGGCGGGTATACCTGGGAGCGAAAAATGACTTATGAGGACGGGGGC					
gi_15081471_	CAGAC-GTTTCCTGAGG--GGTATTCCTGGGAACGAAGCATGACTTACGAAGACCAGGGC					
	250	260	270	280	290	300
seq_29						
gi_15081471_						

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```

          310      320      330      340      350
seq_29      ATAAGTAACGTCCGAAGCGACAT--CAGTG-TGAAAGG-----TGACTCTTTCTACTAT
          ::  :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :
gi_15081471_ ATTTGCGTCGCCACAAACGACATAACACTGATGAAAGGCGTCGATGACTGTTTTGTCTAT
          300      310      320      330      340      350

          360      370      380      390      400
seq_29      AAGATTCACCTTCACTGGCG---AGTTTCCTCCTCATGGTCCAGTGATGCAGAGAAAGACA
          ::  ::  ::  ::  ::  :  ::  :  :  ::  :  :  ::  :  :  ::  :
gi_15081471_ AAAATTCGATTTGATGGTGTAAACTTTCCTGCCAATGGTCCAGTTATGCAAAAGAAGACG
          360      370      380      390      400      410

          410      420      430      440      450      460
seq_29      GTAAATGGGAGCCATCCACTGAAGTAATGTATGTTGACGACAAGAGTGACGGTGTGCTG
          :  ::  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
gi_15081471_ CTGAAATGGGAGCCATCCACTGAGAAAATGTATGT-----GCGTGATGGAGTGCTG
          420      430      440      450      460

          470      480      490      500      510      520
seq_29      AAGGGAGATGTCAACATGGCTCTGTTGCTTAAAGATGGCCGCCATTTGAGAGTTGACTTT
          ::  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
gi_15081471_ AAGGGTGATGTTAACATGGCTCTGTTGCTTGAAGGAGGTGGCCATTACCGATGTGACTTC
          470      480      490      500      510      520

          530      540      550      560      570      580
seq_29      AACACTTCTTACATACCCAAGAAGAAGGTCGAGAATATGCCTGACTACCATTTTATAGAC
          ::  ::  :  :  :  :  :  :  :  :  :  :  :  :  :  :
gi_15081471_ AAAACTACATACAAAGCTAAGAAGTTTGTCCAGT---TGCCAGACTATCACTTTGTGGAC
          530      540      550      560      570      580

          590      600      610      620      630      640
seq_29      CACCGCATTGAGATTCTGGGCAACCCAGAAGA---CAAGCCGGTCAAGCTGTACGAGTGT
          ::  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
gi_15081471_ CATCGCATTGAGATTTTGAGCCACGACAAAGATTACAACAAGGTTAAGCTGTATGAGCAT
          590      600      610      620      630      640

          650      660      670      680
seq_29      GCTGTAGCTCGCTATTCTCTGCTGCCTGAGAAGAACAAGTAG.
          ::  :  :  :  :  :  :  :  :  :  :  :  :  :
gi_15081471_ GCCGAAGCTC---ATTCTGGGCTGCCGAGGCAGGCCAAGTA-
          650      660      670      680

```

Regarding claims 33 and 35, GenBank Accession No. AF401282 teaches a probe comprising at least 10 consecutive bases of a sequence comprising the instant SEQ ID NO: 29 (see alignment following either claim 1 or claim 29). As noted above, the sequence taught by Lesser has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700

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contiguous residues (see alignment presented above following claim 1, where the 206 nucleotide segment taught by Lesser is about 700 residues).

Regarding claim 188, Lesser teaches an isolated, synthetic, or recombinant nucleic acid comprising a sequence encoding a fluorescent protein and having at least about 75% identity to the instant SEQ ID NO: 29 (see alignment following claim 29, where the 70% identity between the Lesser sequence and SEQ ID NO: 29 is about 75%).

Regarding claim 192, the sequence recited in GenBank Accession No. AF401282 encodes a fluorescent protein (see definition) and also has a sequence comprising a combination of segments whose overhangs as described in Figure 15 can anneal to each other. Specifically, the GenBank sequence comprises segments with overhangs that can anneal to each other such as "GGA" which is the start overhang in the segment defined by nucleotides 42-44 and the "stop" overhang in the segment defined by nucleotides 98-100 "CCT" (see alignment following claim 29). Also, as noted above, the sequence taught by Lesser has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 206 nucleotide segment taught by Lesser is about 700 residues).

7. Claims 1, 15, 29, 33, 35, 40, 43-45, 48, 49, 87, 188, 192, and 225-228 are rejected under 35 U.S.C. 102(b) as being anticipated by Lukyanov et al. (WO 01/27150 A2; cited previously).

Regarding claim 1, Lukyanov teaches an isolated, synthetic, or recombinant nucleic acid encoding a fluorescent protein, comprising a nucleic acid sequence having at least 75% sequence identity to the nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues. See the alignment presented below which demonstrates that Lukyanov

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teaches a sequence with 75% identity to the instant SEQ ID NO: 29 over a region of 19 contiguous residues. As noted above, the phrase "at least about 700 contiguous residues" does not define a minimal number of residues that are "at least about 700 contiguous residues." Therefore, the teachings of Lukyanov anticipate the instant claim 1.

78.9% identity in 19 nt overlap; score: 59 E(10,000): 6.5e+03

	190	200
seq_29	ATGGAAACCGTACATTCAC	
	:::: :: :: :: ::	
Lukyanov	ATGGGAACGGTCCATGCAC	
	320	330

Regarding claim 15, the nucleic acid sequence taught by Lukyanov encodes a cyan fluorescent protein (see Table 1, page 29, where the emission maximum of SEQ ID No: 9 (dsFP483 is reported to be 483 nm. This value is within the emission range for cyan fluorescent proteins).

Regarding claim 29, Lukyanov teaches a sequence that is 60% identical to the instant SEQ ID NO: 29 (see alignment below). This sequence inherently hybridizes under stringent conditions to the instant SEQ ID NO: 29. Also, as noted above, the sequence taught by Lukyanov has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 19 nucleotide segment taught by Lukyanov is about 700 residues).

ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
 wipo_seq_9 600 nt vs.
 seq_29 610 nt
 scoring matrix: DNA, gap penalties: -16/-4
 60.0% identity; Global alignment score: 747

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wipo_seq_9	10	20	30	40	50	60
	TCAAGGAAGAAATGTTGATCGATCTTCATCTGGAAGGAACGTTCAATGGGCACACTTTTG					
seq_29	TGAAGGAAGTAATGAAGATCAGTCTGGAGATGGACTGCACCTGTTAACGGCGACAAATTTA					
	10	20	30	40	50	60
wipo_seq_9	70	80	90	100	110	
	AAATAAAAGGCAAAGGAAAAGGGAAGCCTAATGAAGGCACCAATACCGT-CACGCTCGAG					
seq_29	AGATCACTGGGGATGGAACAGGAGAACCTTACGAAGGAACACAGACTTTACATCTTACAG					
	70	80	90	100	110	120
wipo_seq_9	120	130	140	150	160	170
	GTTACCAAGGGTGGACCTCTGCCATTTGGTTGGCATATTTTGTGCCCAATTTTCAGTAT					
seq_29	AGAAGGAAGGCAAG-CCTCTGACGTTTCTTTTCGATGTATTGACACCAGCATTTCAGTAT					
	130	140	150	160	170	
wipo_seq_9	180	190	200	210	220	230
	GGAAACAAGGCATTTGTCCACCACCCTGACGACATACCTGATTATCTAAAGCTGTCA-TT					
seq_29	GGAAACCGTACATTACCAAATACCCAGGCAATATACCAGACTTTTTTCAAGCAGACCGTT					
	180	190	200	210	220	230
wipo_seq_9	240	250	260	270	280	290
	TCCGGAAG-GGATATACATGGGAACGGTCCATGCACTTTGAAGACGGTGGCTTGTGTTGT					
seq_29	TCTGGTGGCGGGTATACCTGGGAGCGAAAAATGACTTATGAGGACGGGGGCATAAGTAAC					
	240	250	260	270	280	290
wipo_seq_9	300	310	320	330	340	350
	ATCACCAATGATATCAGTTTGACAGGCAACTGTTTCAACTACGACATCAAGTTCACTGGC					
seq_29	GTCCGAAGCGACATCAGTGTGAAAGGTGACTCTTTCTACTATAAGATTCACTTCACTGGC					
	300	310	320	330	340	350
wipo_seq_9	360	370	380	390	400	410
	TTGAACTTTCCTCCAAATGGACCCGTTGTGCAGAAGAAGACAACCTGGCTGGGAACCGAGC					
seq_29	GAG---TTTCCTCCTCATGGTCCAGTGATGCAGAGAAAGACAGTAAATGGGAGCCATCC					
	360	370	380	390	400	410
wipo_seq_9	420	430		440	450	460
	ACTGAGCGTTTGTATCCTC-----GTGATGGCGTGTTGATAGGAGACATCCATCAT					
seq_29	ACTGAAGTAATGTATGTTGACGACAAGAGTGACGGTGTGCTGAAGGGAGATGTCAACATG					
	420	430	440	450	460	470
wipo_seq_9	470	480	490	500	510	520
	GCTCTCACAGTGGAAAGGAAGGTGGTT--CATTACGTATGTGACATTAA-ACTGTTTACAG					
seq_29	GCTCT---GTTGCTTAAAGATGGCCGCCATTTGAGAGTTGACTTTAACACTTCTTACAT					
	480	490	500	510	520	530

	530	540	550	560	570	580
wipo_seq_9	GGCCAAGAAGCCCCTAAAGA---TGCCAGGGTATCACTATGTTGACACCAAAGTGGTTAT					
	: : : : : :	: : : :	: : : : :	: : : : :	: : : : :	: : : : :
seq_29	ACCCAAGAAGAAGGTCGAGAATATGCCTGACTACCATTTTATAGACCACCGCATTGAGAT					
	540	550	560	570	580	590
	590	600				
wipo_seq_9	AAGGAGCAACGACAAAGA					
	: : : : :	: : : :				
seq_29	TCTGGGCAACCCAGAAGA					
	600	610				

Regarding claim 40, Lukyanov teaches an amplification primer pair (see page 12, line 32- page 13, line 4) for amplifying a nucleic acid sequence encoding a polypeptide with fluorescent activity (SEQ ID No: 9 of Lukyanov), where the primer pair is capable of amplifying a nucleic acid of claim 1 (Lukyanov teaches a nucleic acid that anticipates claim 1, as noted above).

Regarding claim 43, Lukyanov teaches an expression cassette comprising the nucleic acid of claim 1 (page 10, lines 12-13).

Regarding claim 44, Lukyanov teaches a vector comprising the nucleic acid of claim 1 (page 10, lines 12-17).

Regarding claim 45, Lukyanov teaches that the vector may be a plasmid, phage, or cosmid (page 2, lines 35-36). Lukyanov also teaches the use of viral vectors, phagemids,

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fosmids, bacteriophages, and artificial chromosomes (see page 11, and the cited references therein).

Regarding claims 48 and 49, Lukyanov teaches a transformed cell comprising a vector where the vector comprises a nucleic acid of claim 1 (page 10, line 12 – page 11, line 36).

Regarding claim 87, Lukyanov teaches an array comprising the immobilized nucleic acid of claim 1 (page 13, lines 5-14).

Regarding claim 188, Lukyanov teaches an isolated nucleic acid sequence encoding a fluorescent protein (see above) and having at least about 75% identity to SEQ ID No: 29 (see alignment presented following claim 29, where the sequences are 60% identical over the full-length SEQ ID No: 29. This is about 75% identity).

Regarding claim 192, SEQ ID No: 9 of Lukyanov encodes a fluorescent protein (see above) and also has a sequence comprising a combination of segments whose overhangs as described in Figure 15 can anneal to each other. Specifically, SEQ ID No: 9 of Lukyanov comprises segments with overhangs that can anneal to each other such as GGA which is the “start” overhang in the segment defined by nucleotides 32-34 and the “stop” overhang in the segment defined by nucleotides 135-137 “CCT” (see alignment above). Also, as noted above, the sequence taught by Lukyanov has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 19 nucleotide segment taught by Lukyanov is about 700 residues).

Regarding claims 225 and 226, Lukyanov teaches a recombinant nucleic acid encoding a fluorescent protein codon-optimized for expression in a host cell comprising the sequence of

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claim 1 (SEQ ID NO: 9 of Lukyanov anticipates the instant claim 1, as discussed above; page 14, lines 3-5 and page 36, lines 1-5 teach codon-optimized forms).

Regarding claim 227, Lukyanov further teaches inclusion of a tag or reporter sequence (page 4, lines 10-12) and also the inclusion of epitope tags (page 9, lines 26-34).

Regarding claim 228, Lukyanov teaches labeled probes (page 12, lines 26-28), and further teaches that the nucleic acids may be labeled with epitope tags (page 9, lines 26-34).

8. Claims 1, 15, 29, 40, 43-45, 48, 49, 188, and 192 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US 6,140,132).

Regarding claim 1, Tsien teaches an isolated, synthetic, or recombinant nucleic acid encoding a fluorescent protein, comprising a nucleic acid sequence having at least 75% sequence identity to the nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues. See the alignment presented below which demonstrates that Tsien teaches a sequence with 75% identity to the instant SEQ ID NO: 29 over a region of 17 contiguous residues. As noted above, the phrase "at least about 700 contiguous residues" does not define a minimal number of residues that are "at least about 700 contiguous residues." Therefore, the teachings of Tsien anticipate the instant claim 1.

82.4% identity in 17 nt overlap; score: .58 E(10,000): 6.8e+03

```
          630          640
seq_29  GGTCAAGCTGTACGAGT
        :: : :::::::::: ::
tsien_  GGACGAGCTGTACAAGT
          710
```


Regarding claim 29, Tsien teaches a sequence that is 51% identical to the instant SEQ ID NO: 29 (see alignment below). This sequence inherently hybridizes under stringent conditions to the instant SEQ ID NO: 29. Also, as noted above, the sequence taught by Tsien has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 17 nucleotide segment taught by Tsien is about 700 residues).

```
ALIGN calculates a global alignment of two sequences
  version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
seq_29                                     687 nt vs.
tsien_cfp_seq_7                           720 nt
scoring matrix: DNA, gap penalties: -16/-4
49.0% identity;      Global alignment score: -11
```

		10		20		30		40	
seq_29	ATG-----AAGGGGGTGAAG-----GAAGTAATGAAGATCAGTCTGGAGATGGAC								
	::: ::: :: : : :: : :: :: :: : :: :: :::								
tsien_cfp_se	ATGGTGAGCAAGGGCGAGGAGCTGTTACCGGGGTGGTGCCCATCCTGGTCGAGCTGGAC								
		10	20	30	40	50	60		
		50	60	70	80	90	100		
seq_29	TGCACTGTTAACGGCGACAAATTTAAGATCACTGGGGATGGAACAGGAGAACCTTACGAA								
	:: ::								
tsien_cfp_se	GGCGACGTAAACGGCCACAGGTTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTAC								
		70	80	90	100	110	120		
		110	120	130	140	150	160		
seq_29	GGAACACAGACTTTACATCTTACAGAGAAGGAAGGCAAGCCTCTGACGTTTTCTTTCGAT								
	:: : : :: :								
tsien_cfp_se	GGCAAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCC--CGTGCCCTGGCCCA								
		130	140	150	160	170			
		170	180	190	200	210	220		
seq_29	GTATTGACACCAGCATTTTCAGTATGGAAACCGTACATTACCAAATACCCAGGCAATAT-								
	: : :: :: :								
tsien_cfp_se	CCCTCGTGACCACCTGACCTGGGGCGTGCAGTGC-TTCAGCCGCTACCCCGACCACATG								
	180	190	200	210	220	230			

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```

                230      240      250      260      270
seq_29      -ACCAG---ACTTTTCAAGCAGACCGTTTCTGGTGGCGGGTATACCTGGGAGCGAAAA
            :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :  ::  :
tsien_cfp_se AAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGC---TACGTCCAGGAGCGCACC
            240      250      260      270      280      290

                280      290      300      310      320      330
seq_29      ATGACTTATGAGGACGGGGGCATAAGTAACGTCCGAAGCGACATCAGTGTGAAAGGTGAC
            ::  :  :  ::  :  :  ::  :  :  ::  :  :  :  :  :  :  :  :
tsien_cfp_se ATCTTCTTCAAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGAC
            300      310      320      330      340      350

                340      350      360      370      380      390
seq_29      TCTTTCTACTATAAGATTCACTTCA--CTGGCGAGTTTCCTCCTCATGGTCCAGTGATGC
            :  ::  :  :  ::  :  :  :  ::  :  :  :  ::  :  :  :  :  :
tsien_cfp_se AC--CCTGGT----GAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAAC
            360      370      380      390      400

                400      410      420      430      440
seq_29      AGAGAAAGACAGTAAAATGGGAGCCATCCACTGAAGT---AATGTATGTT-----GACGA
            :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
tsien_cfp_se ATCCTGGGGCAC-AAGCTGGAGTACAACATCAGCCACAACGTCTATATCACCGCCGA
            410      420      430      440      450      460

                450      460      470      480      490      500
seq_29      CAAGAGTGACGGTGTGCTGAAGGGAGATGTCAACATGGCTCTGTTGCTTAAAGATGGCCG
            ::  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
tsien_cfp_se CAAGCAGAAGAACGGCATCAAGGCCCACTTCAAGATCCGCCACAACATCGAGGACGGCAG
            470      480      490      500      510      520

                510      520      530      540      550      560
seq_29      CCATTTGAGAGTTGACTTTAACTTCTTACATACCCAA-GAAGAAGGTC--GAGAATAT
            :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
tsien_cfp_se CGTGCAGCTCGCCGACCACTACCAGCAGAACACCCCATCGGCGACGGCCCCGTGCTGCT
            530      540      550      560      570      580

                570      580      590      600      610      620
seq_29      GCCTGACTACCATTTTATAGACCACCGCATTGAGATTCTGGGCAA---CCCAGAAGACAA
            :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
tsien_cfp_se GCCCCACAACCACTACCT-GAGCACC-CAGTCCGCC-CTGAGCAAAGACCCCAACGAGAA
            590      600      610      620      630      640

                630      640      650      660      670
seq_29      GC-CGGTCAAGCTGTAC-----GAGT--GTG-CTGTAGCTCGCTAT---TCTCTGC-TGC
            :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :  :
tsien_cfp_se GCGCGATCACATGGTCCTGCTGGAGTTTCGTGACCGCCGC-CGGGATCACTCTCGGCATGG
            650      660      670      680      690      700

                680
seq_29      CTGAGAAGAACAAGTAG
            :  :  :  :  :  :
tsien_cfp_se ACGAGCTGTACAAGTAA
            710      720

```

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Regarding claim 40, Tsien teaches an amplification primer pair for amplifying a nucleic acid sequence encoding a polypeptide with fluorescent activity (column 11, lines 41-46), where the primer pair is capable of amplifying a nucleic acid of claim 1 (Tsien teaches a nucleic acid that anticipates claim 1, as noted above).

Regarding claim 43, Tsien teaches an expression cassette comprising the nucleic acid of claim 1 (column 11, line 57 – column 12, line 40).

Regarding claim 44, Tsien teaches a vector comprising the nucleic acid of claim 1 (column 11, line 66 – column 12, line 40).

Regarding claim 45, Tsien teaches that the vector may be a plasmid, phage, cosmid viral vectors, bacteriophages, and artificial chromosomes (column 13, lines 45-63).

Regarding claims 48 and 49, Tsien teaches a transformed cell comprising a vector where the vector comprises a nucleic acid of claim 1 (column 13, lines 45-63).

Regarding claim 188, Tsien teaches an isolated nucleic acid sequence encoding a fluorescent protein (see above) and having at least about 75% identity to SEQ ID No: 29 (see alignment presented following claim 29, where the sequences are 49% identical over the full-length SEQ ID No: 29. This is about 75% identity).

Regarding claim 192, SEQ ID No: 7 of Tsien encodes a fluorescent protein (see above) and also has a sequence comprising a combination of segments whose overhangs as described in Figure 15 can anneal to each other. Specifically, SEQ ID No: 7 of Tsien comprises segments with overhangs that can anneal to each other such as GGA which is the “start” overhang in the segment defined by nucleotides 18-20 and the “stop” overhang in the segment defined by nucleotides 116-118 “CCT” (see alignment following claim 29). Also, as noted above, the

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sequence taught by Tsien has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 17 nucleotide segment taught by Tsien is about 700 residues).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 217 and 218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lukyanov et al. (WO 01/27150; cited previously) in view of Short (WO 00/77262 A1; cited previously).

Lukyanov teaches a nucleic acid sequence (SEQ ID NO: 9) that anticipates the instant claim 1, as discussed above.

Lukyanov teaches that the nucleic acid may be obtained using non-stochastic site-directed mutagenesis methods (page 13, line 15 – page 14, line 2), but does not teach generation of the recombinant nucleic acid by synthetic ligation reassembly.

Regarding claim 218, Lukyanov teaches expression of recombinant proteins (page 13, line 15 – page 14, line 2).

Short teaches a directed evolution method for evolving nucleic acids encoding novel or improved proteins (see abstract).

Regarding claim 217, Short teaches that standard non-stochastic mutagenesis methods are limited, because only a small number of new variant products are generated with each application of the methods and the types of mutations possible are also limited (see page 4, lines 15-20). Short teaches that synthetic ligation reassembly represents an improvement over these standard non-stochastic site-directed mutagenesis methods, because: (1) it generates a larger number of products with predetermined (non-random) structures with each application; (2) it readily generates more types of mutant polynucleotides, thereby generating a resulting group of mutant products with greater diversity; (3) background resulting from undesired products is decreased; (4) saturation or exhaustive mutagenesis is possible; and (5) the products are produced in a systematic, predetermined fashion (see page 5, lines 1-10).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the synthetic ligation reassembly method taught by Short to generate recombinant versions of the nucleic acids of Lukyanov. Lukyanov expressly taught production of recombinant polynucleotides using site-directed mutagenesis techniques in order to obtain polynucleotides encoding proteins with improved properties (see page 13, lines 13-31). Since

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Short taught that synthetic ligation reassembly offered distinct advantages over the conventional methods suggested by Lukaynov, namely the ability to more efficiently and accurately generate a larger number of different, more diverse product sequences (see above), the ordinary practitioner would have been motivated to utilize this method in order to obtain a faster, simpler method of generating a large variety of mutant polynucleotides.

Allowable Subject Matter

11. Claim 189 is allowed.

Response to Arguments

12. Claim Objections

Applicant's arguments, see page 17, filed October 16, 2006, with respect to the objections to claims 219 and 220 have been fully considered and are persuasive. These objections have been withdrawn.

Rejections under 35 U.S.C. 112, 1st paragraph

Applicant's arguments filed October 16, 2006 have been fully considered but they are not persuasive. Applicant argues that the disclosure teaches a representative number of species, and particularly cites those sequences recited in the instant claims 215, 216, 220, 224, and 229 as exemplary sequences within the claimed genus. This argument was not found persuasive, because although these claims disclose numerous sequences with identity to SEQ ID NO: 29 ranging from 72% (SEQ ID NO: 169 disclosed in claim 224) to 99.6% (SEQ ID NO: 17,

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disclosed in claim 208), the functional properties of the vast majority of the proteins encoded by these different sequences have not been determined. As noted above, the fluorescence properties of only two proteins (SEQ ID NO: 8 and SEQ ID NO: 18) were measured by fluorescence spectroscopy (See Figures 11-14). Also, Table 2 in the specification recites excitation and emission wavelengths for a number of proteins encoded by nucleic acid sequences of the invention, but it is not clear whether these are predicted or experimentally determined values. As discussed above, an enormous number of sequences (7.2×10^{274}) possess 75% identity to the instant SEQ ID NO: 29 over 700 contiguous residues. Although Applicant has demonstrated possession of the genus of nucleic acid sequences displaying at least 95% identity to the instant SEQ ID NO: 29, Applicant has not demonstrated possession of the claimed genus of sequences having only 75% identity to the instant SEQ ID NO: 29. Therefore, the rejection of claims 1, 14, 15, 29, 33, 35, 40, 43-45, 48, 49, 87, 188, 192, 203-207, 217, 218, and 225-228 as lacking adequate written description under § 112, 1st paragraph has been maintained.

Rejections under 35 U.S.C. 102

Applicant's arguments filed October 16, 2006 have been fully considered but they are not persuasive. Applicant argues that none of the previously applied references (Lesser, Lukaynov, Tsien) teach all of the elements of the amended claims (see pages 19-20 of the response). This argument was not found persuasive, because as discussed above, the phrase "at least about 700 contiguous residues" appearing in amended claim 1 and the phrase "at least about 75% identity" appearing in claim 188 renders these claims indefinite. The use of the phrase "at least about" results in complete uncertainty as to the minimum number of contiguous residues or percent

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identity encompassed by the claims, and the specification does not cure this deficiency by explicitly defining these phrases. Therefore, in the absence of a clearly defined minimum boundary for the required percent identity or stretch of contiguous residues, the prior art of Lesser, Lukaynov, and Tsien continues to anticipate the instant claims. These rejections are maintained.

Rejections under 35 U.S.C. 103

Applicant's arguments filed October 16, 2006 have been fully considered but they are not persuasive. Applicant argues that Lukaynov does not teach all of the elements of the amended claim 1 and Short does not remedy this deficiency in the primary reference (page 20 of the response). This argument was not found persuasive, because as discussed above, the Lukaynov does teach a nucleic acid anticipating the instant claim 1. The Short reference is only relied upon for its teachings regarding synthetic ligation reassembly. Therefore, the rejection of claims 217 and 218 as obvious in view of the combined teachings of Lukaynov and Short is maintained.

Conclusion

With the exception of claim 189 (allowable over the art), the claims are free of the art, but have been rejected for other reasons, as noted above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
December 18, 2006

amb


JEFFREY FREDMAN
PRIMARY EXAMINER
12/20/06